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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/553,595

10/19/2005

Steven Ledbetter

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04/13/2009

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EXAMINER

ROMEO, DAVID S

ART UNIT

PAPER NUMBER

1647

MAIL DATE

DELIVERY MODE

04/13/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/553,595	Applicant(s) LEDBETTER ET AL.	
	Examiner David S. Romeo	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 December 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,5,7-25,27,29-35 and 37-39 is/are pending in the application.
- 4a) Of the above claim(s) 9,11,12,20,21,27,31,33 and 34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,5,7,8,10,13-19,22-25,29,30,32,35 and 37-39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-3,5,7-25,27,29-35 and 37-39 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The amendment filed 12/22/2008 has been entered. Claims 1, 2, 3, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 29, 30, 31, 32, 33, 34, 35, 37, 38, 39 are pending.

5

Election/Restrictions

Applicant's elected without traverse an anti-TGF β antibody in the reply filed on 03/10/2008.

Applicant's elected with traverse 1D11, lisinopril and renal insufficiency in the reply filed on 03/10/2008.

10

The requirement was deemed proper and was therefore made FINAL.

Claims 9, 11, 12, 20, 21, 27, 31, 33 and 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 03/10/2008.

15 **Maintained formal matters, objections, and/or rejections:**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

20

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

25

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1–3, 13–19, 22–25, 35, 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Border (Hypertension. 1998 Jan;31(1 Pt 2):181-8) and Reeves (Proc Natl Acad Sci U S A. 2000 Jul 5;97(14):7667-9).

5 Applicants argue that:

10 ...the generalized teachings in Border and Reeves ...do not immediately suggest the claimed method (i.e., limited to a method employing an anti-TGF β antibody and an ACE inhibitor). ...neither suggests the specific method claimed, nor provides a reasonable expectation of achieving the treatment efficacy shown by Applicants

15 ... the combined teachings of Border and Reeves would lead the skilled artisan to expect that a dual therapy targeting both the RAS pathway and the TGF β pathway would result in only a minor, if any, improvement in therapeutic effect over each individual treatment. ...Border teaches away from the claimed method because it suggests that administration of an ACE inhibitor with a TGF β antagonist could actually interfere with the TGF β lowering effects of the TGF β antagonist treatment.

20 ...one of skill in the art would not expect co-administration of an anti-TGF β antibody with an ACE inhibitor to achieve the surprising efficacy in improvement of therapeutic endpoints that Applicants have demonstrated.

25 Applicants' arguments have been fully considered but they are not persuasive. Border teaches:

30 ...the current pharmacological approaches to block the RAS are suboptimal and that, in addition to blood pressure, normalization of TGF β should be part of the therapeutic goal. Current evidence suggests that a combination of RAS blockade with a separate agent to suppress TGF- β may be superior to RAS blockade alone. Such a combination may be required if progressive fibrotic diseases, such as diabetic nephropathy, are to be truly prevented, instead of just delayed.

Paragraph bridging pages 181-182.

35 ...in renal fibrotic diseases, therapies aimed at more than one arm [of the RAS and TGF β systems] will be necessary to effectively halt, rather than merely slow, disease.

Page 186, right column, full paragraph 1.

The examiner concludes that Border clearly suggest a combination of TGF β suppression/normalization and RAS blockade for the treatment of renal diseases. Border also discloses enalapril, an ACE inhibitor (paragraph bridging pages 182-183) designed for RAS blockade, and neutralizing antibody to TGF β (page 184, paragraph bridging left and right columns), an agent designed for TGF β suppression. Border's suggestion to combine RAS blockade with a separate agent to suppress TGF- β provides strong evidence of obviousness in combining them for their intended purposes. One of ordinary skill in the art would be motivated to make this combination because the current pharmacological approaches to block the RAS are suboptimal and that, in addition to blood pressure, normalization of TGF β should be part of the therapeutic goal, as taught by Border. Border's suggestion that the combination may be superior to RAS blockade alone provides strong evidence that the alleged unexpected benefits shown by applicants are not unexpected. Although one of ordinary skill in the art may not have been able to predict with absolute certainty the precise quantitative results from such a combination, obviousness does not require absolute predictability, only a reasonable expectation of success, i.e., a reasonable expectation of obtaining similar properties. Border's suggestion that the combination may be superior to RAS blockade alone provides a reasonable expectation of obtaining similar properties.

Furthermore, the fact that Angiotensin blockade only partially decreases TGF β expression (Border, Table, page 184) and the fact that ACE inhibition therapies have been designed with blood pressure reduction as their target (Border, page 183, right column, full paragraph 3) would lead one of ordinary skill in the art to expect a greater effect by combining

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TGF β antagonism with ACE inhibition than either treatment alone because one of ordinary skill in the art would expect the beneficial effects of both blood pressure reduction and TGF β suppression.

Border's teaching that treatment of rats with enalapril, and ACE inhibitor, further increased the expression of TGF β in the JGA (paragraph bridging pages 182-183) could also be construed as further motivation to combine RAS blockade with TGF- β suppression in order to overcome increased TGF β expression in the JGA that may result from ACE inhibition.

Furthermore, Border explicitly suggest combining RAS blockade with TGF- β suppression.

Furthermore, angiotensin blockade only partially decreases TGF β expression (Table, page 184).

Furthermore, ACE inhibition therapies have been designed with blood pressure reduction as their target (Border, page 183, right column, full paragraph 3). One of ordinary skill in the art could reasonably expect to achieve blood pressure reduction with ACE inhibition and TGF β suppression with anti-TGF β neutralizing antibodies. Furthermore, Border teaches that "...in renal fibrotic diseases, therapies aimed at more than one arm [of the RAS and TGF β systems] will be necessary to effectively halt, rather than merely slow, disease." Page 186, right column, full paragraph 1. Therefore, the examiner does not believe that Border teaches away from the claimed invention.

Claims 1-3, 7, 8, 10, 13-19, 22-25, 29, 30, 32, 35, 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Border (Hypertension. 1998 Jan;31(1 Pt 2):181-8) and Reeves (Proc Natl Acad Sci U S A. 2000 Jul 5;97(14):7667-9) as applied to claims 1-3, 13-19, 22-25, 35, 37 and 38 above and further in view of Ledbetter (WO 01/66140).

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Applicants argue that:

Ledbetter ...does not disclose the use of ACE inhibitors. Accordingly, Ledbetter does not cure the defects of the combined teachings of Border and Reeves

5 Applicants' arguments have been fully considered but they are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

10 As discussed above, Border's suggestion that the combination of RAS blockade and TGF β suppression may be superior to RAS blockade alone provides strong evidence that the alleged unexpected benefits shown by applicants are not unexpected.

Claims 1-3, 5, 7, 8, 10, 13-19, 22-25, 29, 30, 32, 35, 37 and 38 are rejected under 35
15 U.S.C. 103(a) as being unpatentable over Border (Hypertension. 1998 Jan;31(1 Pt 2):181-8) and Reeves (Proc Natl Acad Sci U S A. 2000 Jul 5;97(14):7667-9) and further in view of Ledbetter (WO 01/66140) as applied to claims 1-3, 7, 8, 10, 13-19, 22-25, 29, 30, 32, 35, 37 and 38 above and further in view of Agarwal (Am J Kidney Dis. 2002 Mar;39(3):486-92).

Applicants argue that:

20 Agarwal ...does not teach the combination of TGF β antagonists with RAAS inhibitors in general, let alone the instantly claimed combination therapy using an anti-TGF β antibody and an ACE inhibitor. Further, Agrawal adds nothing to the combined teachings of Border and Reeves Accordingly, Agrawal does not
25 cure the defects in the combined teachings of Border and Reeves, either with or without the further teachings of Ledbetter.

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Applicants' arguments have been fully considered but they are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re*
5 *Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

As discussed above, Border's suggestion that the combination of RAS blockade and TGF β suppression may be superior to RAS blockade alone provides strong evidence that the alleged unexpected benefits shown by applicants are not unexpected.

New Formal Matters, Objections and/or Rejections

10 The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

15 The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1–3, 5, 7, 8, 13–19, 22–25, 29, 30, 35, 37 and 38 are rejected under 35
U.S.C. 112, first paragraph, because the specification, while being enabling for a method
20 comprising administering a therapeutically effective amount of a TGF β antagonist wherein the antagonist is an anti-TGF β antibody, does not reasonably provide enablement for a method comprising administering a therapeutically effective amount of an anti-TGF β antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

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The claims are directed to a method of treatment comprising administering a therapeutically effective amount of an anti-TGF β antibody. The claims do not require that the anti-TGF β antibody neutralize or antagonize TGF β activity. The term “therapeutically effective amount” encompasses and/or implies alleviating or treating renal insufficiency. However, as a skilled practitioner would appreciate, blocking a particular epitope does not necessarily neutralize the functional activity of the protein to which the antibody is directed. See, for example, Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63), paragraph bridging pages 1056-1057. The specification lacks guidance for, and working examples of, neutralizing or antagonizing TGF β activity with an non-neutralizing or non-antagonizing anti-TGF β antibody. The examiner is aware working examples are not required. Lack of a working example is, however, a factor to be considered. In view of the breadth of the claims and the limited amount of direction and working examples provided by the inventor, it would require undue experimentation for the skilled artisan to make and use the full scope of “a therapeutically effective amount of an anti-TGF β antibody” that is non-neutralizing or non-antagonizing.

Claims 10, 32 and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1D11, does not reasonably provide enablement for ATCC Designation No. HB9849. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

ATCC Deposit No. HB9849 is required in order to make and/or use the claimed invention. The deposit rules (37 CFR 1.801 - 1.809) set forth conditions of deposit which must

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be satisfied in the event a deposit is required. 37 C.F.R. § 1.808(a)(2) requires that a deposit must be made under conditions that assure that, subject to paragraph (b) of this section, all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent. According to M.P.E.P. 2410.01, the mere indication that a deposit has been made under conditions prescribed by the Budapest Treaty would satisfy all conditions of these regulations except the requirement that all restrictions on access be removed on grant of the patent.

The mere indication that a deposit has been made under conditions prescribed by the Budapest Treaty would not satisfy the requirement that all restrictions on access be removed on grant of the patent. A provision that, with the one possible exception in 37 CFR 1.808(b), all restrictions on the accessibility of the deposit will be irrevocably removed by the applicant upon the granting of a patent is required.

Claim Rejections - 35 USC § 103

Claims 1–3, 5, 7, 8, 10, 13–19, 22–25, 29, 30, 32, 35 and 37–39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Border (Hypertension. 1998 Jan;31(1 Pt 2):181-8) and Reeves (Proc Natl Acad Sci U S A. 2000 Jul 5;97(14):7667-9) and further in view of Ledbetter (WO 01/66140) and further in view of Agarwal (Am J Kidney Dis. 2002 Mar;39(3):486-92) as applied to claims 1–3, 5, 7, 8, 10, 13–19, 22–25, 29, 30, 32, 35, 37 and 38 above, and further in view of Winter (U. S. Patent No. 5,225,539) and Hebert (U. S. Patent No. 5,356,775).

Border and Reeves and further in view of Ledbetter and further in view of Agarwal teach treating a mammal having diminished renal function, slowing loss of renal function in a mammal having a renal disorder or improving renal function in a mammal having diminished renal

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function, by administering to the mammal a therapeutically effective amount of a TGF β antagonist and a therapeutically effective amount of an ACE inhibitor, wherein the TGF β antagonist is an anti-TGF β antibody, wherein the anti-TGF β antibody is a human anti-TGF β antibody, a humanized anti-TGF β antibody, 1D11 or a humanized derivative of 1D11.

5 Border and Reeves and further in view of Ledbetter and further in view of Agarwal are silent regarding a humanized or human antibody comprising CDR sequences identical to those of 1D11, wherein 1D11 is the antibody deposited with the ATCC under the Accession No. HB9849.

10 Winter provides an altered antibody in which at least parts of the CDRs in the light or heavy chain variable domains have been replaced by the analogous CDRs from an antibody of different specificity. The entire CDRs may be replaced. For instance, the CDRs from a mouse antibody could be grafted onto the framework regions of a human antibody. This arrangement will be of particular use in the therapeutic use of monoclonal antibodies. Only the CDRs of the antibody will be foreign to the body, and this should minimize side effects if used for human
15 therapy. See column 3, lines 27-68.

 Winter does not teach treating a mammal having diminished renal function, slowing loss of renal function in a mammal having a renal disorder or improving renal function in a mammal having diminished renal function, by administering to the mammal a therapeutically effective amount of a TGF β antagonist and a therapeutically effective amount of an ACE inhibitor,
20 wherein the TGF β antagonist is an anti-TGF β antibody, wherein the anti-TGF β antibody is a human anti-TGF β antibody, a humanized anti-TGF β antibody, 1D11 or a humanized derivative of 1D11.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to treat a mammal having diminished renal function, slow loss of renal function in a mammal having a renal disorder or improve renal function in a mammal having diminished renal function, by administering to the mammal a therapeutically effective amount of a TGF β antagonist and a therapeutically effective amount of an ACE inhibitor, wherein the TGF β antagonist is an anti-TGF β antibody, wherein the anti-TGF β antibody is a human anti-TGF β antibody, a humanized anti-TGF β antibody, 1D11 or a humanized derivative of 1D11, as taught by Border and Reeves and further in view of Ledbetter and further in view of Agarwal, and to modify that teaching by grafting the CDRs from a mouse antibody onto the framework regions of a human antibody, as taught by Winter, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to graft the CDRs from the mouse 1D11 antibody onto a human antibody because only the CDRs of the antibody will be foreign to the body, and this should minimize side effects if used for human therapy.

It is generally appreciated in the art that humanized forms of antibodies may be generated using CDR grafting. See, for example, Hebert, column 10, lines 50-53. Therefore, Border and Reeves and further in view of Ledbetter and further in view of Agarwal and further in view of Winter and Hebert teach a humanized or human antibody comprising CDR sequences identical to those of 1D11, wherein 1D11 is the antibody deposited with the ATCC under the Accession No. HB9849.

The invention is prima facie obvious over the prior art.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, MANJUNATH RAO, CAN BE REACHED AT (571)272-0939.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE [HTTP://PAIR-DIRECT.USPTO.GOV](http://PAIR-DIRECT.USPTO.GOV). CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

/DAVID S ROMEO/
PRIMARY EXAMINER, ART UNIT 1647